International Workshop of the Oswaldo Cruz Institute/FIOCRUZ for Leptospirosis Research Based on Country Needs
&
5th Global Leptospirosis Environmental Action Network (GLEAN) Meeting

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Leptospirosis: Human case management

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Manejo de Casos en Humanos

Necesidades

By analyzing the main needs of the countries, the issues that are most important are: :

1. **Training medical and nursing staff to perform the diagnosis and treatment.**
2. Being able to conduct clinical trials in the decentralized regions to ensure early diagnosis.
3. The need to update, reproduce and inform about leptospirosis standards.
4. Research and health education about the disease
5. Include the issue of leptospirosis in the pensum of students that will be doing clinical work.
6. **Ensure the timely implementation of treatment.**
7. Strengthen the capacity of laboratory diagnosis.

Leptospirosis : Management

- Wide clinical spectrum of disease severity
- Most cases are uncomplicated, anicteric disease with around 10 days of fever and a low mortality of less than 1%.
- Uncomplicated disease is therefore a major cause of morbidity
- Rapid, reliable laboratory diagnosis is not widely available

Severe Leptospirosis

- High mortality (10- >50%)
- Initial manifestations are nonspecific, similar to other common tropical infections, such as dengue infection, scrub typhus and sepsis from other pathogens

Leptospirosis: Management

- Non-severe leptospirosis
  - ↓ morbidity; shortening duration of illness
  - prevent complication?
- Severe leptospirosis
  - ↓ morbidity and mortality

- ↑ Awareness >> early diagnosis
- Empirical therapy
- Aggressive supportive treatment

WHO recommended surveillance case definition of leptospirosis

"A suspected case"
acute febrile illness; headache, myalgia and prostration; associated with any of the following symptoms:
- conjunctival suffusion
- meningeal irritation
- anuria, oliguria, or proteinuria
- jaundice
- hemorrhage (from intestines; lung bleeding often notorious)
- cardiac arrhythmia or failure
- skin rash
- a history of exposure to infected animals or an environment contaminated with infected animal urine.

WHO. Leptospirosis. Communicable Disease Epidemiological Profile. Geneva: World Health Organization; 2010. pp. 102–108.

CLINICAL PROFILE OF PATIENTS DIAGNOSED WITH LEPTOSPIROSIS AFTER A TYPHOON: A MULTICENTER STUDY

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Abstract. This study described the clinical features and complications of leptospirosis among patients seen at nine tertiary hospitals from September 28 to November 30, 2009 after a heavy rainfall typhoon. The clinical findings of the confirmed cases were compared with the previous clinical studies on seasonal leptospirosis in the Philippines. Risk factors for complicated disease were also identified. Confirmed cases were based on any of the following: positive leptospiral cultures of blood or urine, single high leptospira microscopic agglutination test (MAT) titer of 1:1,600, a fourfold rise in MAT, and/or seroconversion. Of 670 patients with possible leptospirosis, 591 were probable by the WHO criteria, 259 (44%) were confirmed. Diagnosis was confirmed by MAT 176 (68%), by culture 57 (22%), and by MAT and culture 26 (10%). The mean age of the confirmed cases was 38.9 years (SD 14.3). The majority were males (82%) and had a history of wading in floodwaters (98%). The majority of the patients presented with nonspecific signs, with fever as the most common (98.5%). Other findings were myalgia (78.1%), malaise (74.9%), conjunctival suffusion (59.3%), oliguria (56.6%), diarrhea (39%), and jaundice (38%). Most of the patients presented with a moderate-to-severe form of leptospirosis (83%). Complications identified were renal failure (82%), pulmonary hemorrhage (8%), meningitis (5%), and myocarditis (4%). Mortality rate was 5%, mostly due to pulmonary hemorrhage. This study emphasizes the importance of public awareness and high index of suspicion among clinicians of leptospirosis during the monsoon months when flooding is common. Early recognition and detection of the disease should decrease morbidity and mortality.

South East Asian J Trop Med Pub Health, 2013

Table 1

Demographic profile and distribution of confirmed leptospirosis patients (*N*=259

Characteristic	Confirmed
Age (yrs), Mean (±SD)	38.9 (SD 14.3)
Sex, *n* (%)	
Male	213 (82.0)
Female	46 (18.0)
Occupation, *n* (%)	
Unemployed	161 (62.0)
Employed	92 (36.0)
Student	6 (2.0)
Comorbidities, *n* (%)	49 (18.9)
Waded/Swam in flood waters, *n* (%)	253 (98.0)
Swallowed flood water, *n* (%)	58 (22.4)
Presence of wound, *n* (%)	95 (37.3)
Exposure to animal carcass, *n* (%)	39 (15.0)
Duration of illness before admission, *n* (%)	
<7 dys	196 (75.7)
≥7 dys	57 (22.0)
Hospital admission, *n* (%)	
Ward	231 (89.2)
ICU	27 (10.5)
OPD	1 (0.4)
Hospital stay (days)	3 (SD 3.26)

Between Sep 28- Nov 30 2009: 9 tertiary Hospital

670 possible → 591 WHO probable Lepto→259 (38.6%) confirmed leptospirosis

Table 3
Clinical and laboratory features of confirmed leptospirosis cases (*N*=259).

Characteristic	Confirmed *n* (%)
Non-specific	
Fever	255 (98.5)
Myalgia/calf tenderness	200 (78.1)
Malaise	194 (74.9)
Headache	144 (55.6)
Chills	116 (44.8)
Conjunctival suffusion	153 (59.3)
Hypotension	61 (23.6)
Gastrointestinal	
Nausea/Vomiting	136 (52.7)
Abdominal pain	133 (52.0)
Diarrhea	101 (39.0)
Jaundice	98 (38.0)
GI bleeding	41 (16.1)
Renal	
Oliguria	145 (56.6)
Hematuria	57 (22.3)
Pulmonary	
Cough	78 (30.5)
Dyspnea	56 (21.6)
Crackles/rales	60 (23.3)
Hemoptysis	38 (14.9)
Hematologic	
Hemorrhagic signs (epistaxis, petechiae) laboratory	36 (14.6)
Thrombocytopenia (<100,000/mm^3)	44 (17.0)
Leukocytosis (wbc>12,000)	117 (45.2)
Elevated creatinine (>176 µmol/l)	164 (63.8)
Elevated AST (> 37 SI Units)	86 (33.3)
Elevated serum K (>4)	40 (15.4)
Elevated blood urea nitrogen (>10-20 mg/dl)	139 (57.0)

Complications	Mortality *n*=14 (%)
Renal failure	12 (86.0)
Upon admission	11 (78.6)
Progression	1 (7.0)
Pulmonary hemorrhage	10 (71.4)

Overall mortality 5%

Wijesinghe et al. BMC Res Notes (2015) 8:348
DOI 10.1186/s13104-015-1321-7

BMC Research Notes

CASE REPORT Open Access

Fatal co-infection with leptospirosis and dengue in a Sri Lankan male

Aruna Wijesinghe*, Nanthini Gnanapragash, Gayan Ranasinghe and Murugapillai K Ragunathan

Abstract

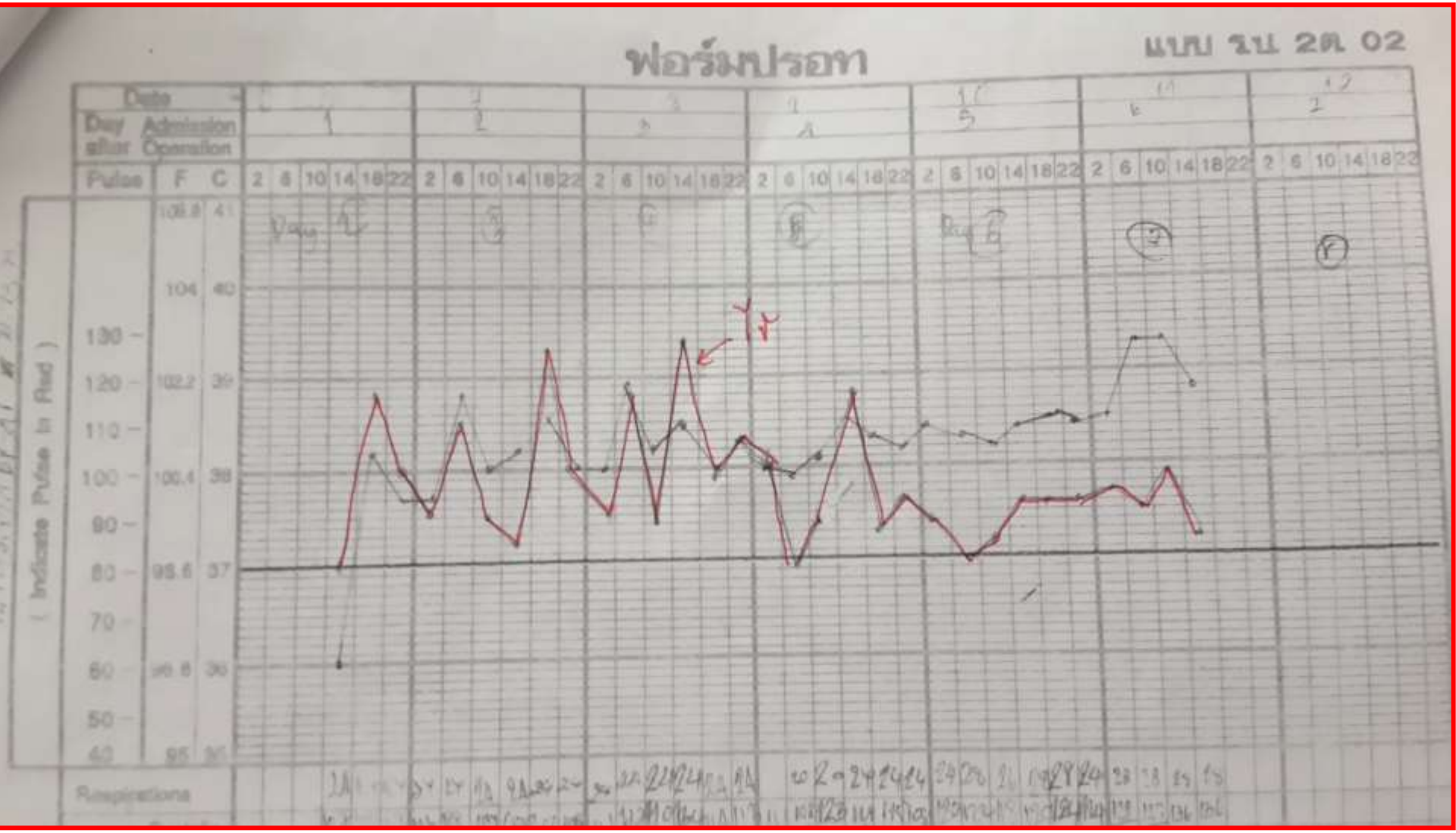
Background: Leptospirosis and dengue are endemic in countries with subtropical or tropical climates and have epidemic potential. The incidence of both these diseases peaks during monsoons and both diseases present with similar clinical manifestations making differentiation of leptospirosis from dengue difficult. It is important to distinguish leptospirosis from dengue as early antibiotic therapy in leptospirosis leads to a favourable outcome, while dengue has no specific treatment, yet early recognition is vital for close monitoring and careful fluid management. Despite the high prevalence of both these infections, co-infection of leptospirosis and dengue has not been reported previously in Sri Lanka. We present the first case of co-infection with leptospirosis and dengue in a Sri Lankan male.

Case presentation: A 52 year old previously healthy Sri Lankan male was admitted to our facility with a history of fever for 4 days associated with headache, generalized myalgia, reduced urine output. On examination, he was rational, hypotensive, tacycardic, tacypneic and he did not have clinical evidence of fluid leakage or pneumonitis. His serology showed high titre of dengue IgG and IgM and rising titre of leptospirosis antibody. His course of illness was complicated with septic shock, acute renal failure, acute respiratory distress syndrome and disseminated intravascular coagulation and he succumbed to his illness on the eighth day of admission.

Conclusion: In areas where both leptospirosis and dengue are endemic, both infections should be include in the differential diagnosis when evaluating patients with acute febrile illness and should consider the possibility of co-infection. Leptospirosis, being a condition having definitive antibiotic therapy, should always be ruled out even if the patient is positive for dengue serology in regions endemic to both these diseases as early initiation of antibiotic therapy can reduce mortality significantly.

Keywords: Dengue fever, Leptospirosis, Co-infection

72 yr Man Fever 1 d



Complete Blood Count

Date	6/10/58	7/10/58	8/10/58	9/10/58	10/10/58	11/10/58
Hb/Hct	12.2/36.5	11.2/33.4	11.0/32.2	11.5/33.9	11.5/33.9	11.6/34.1
WBC	6,830	6,200	5,600	6,800	7,800	9,500
N	89.8	86.5	86.1	82.8	86.0	84.0
L	6.8	7.9	7.5	8.6	5.6	5.8
M	2.5	4.5	4.9	7.1	6.5	7.9
Plt	93,000	74,000	64,000	39,000	40,000	71,000
MCV	93.0	91.0	91.0	91.0	92.0	92.0
RDW	11.3					

Liver test

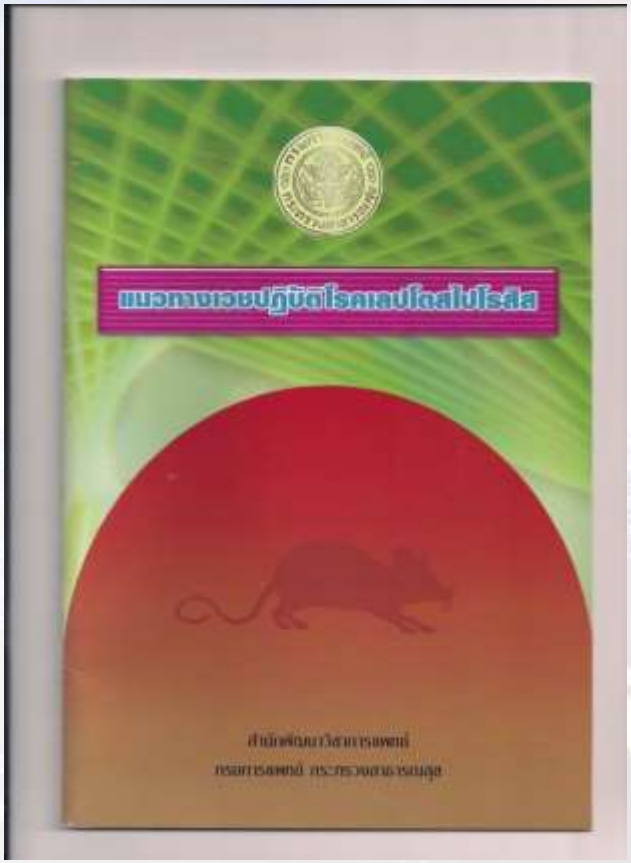
Date	9/10/58	11/10/58
T/D	2.7	8.4
SGOT	46	52
SGPT	41	50
ALP	120	117
Albumin	2.7	2.5
Globulin		

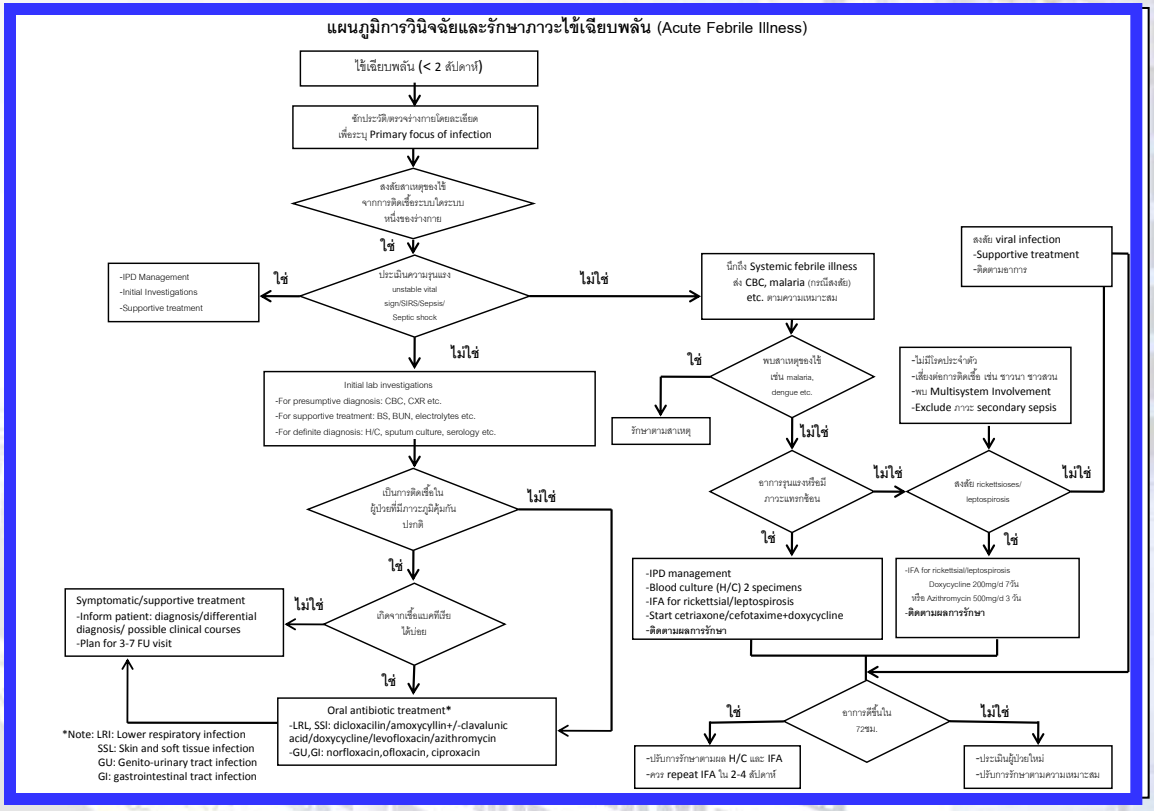
	17-10-15 11:22	18-10-15 05:55	19-10-15 06:15	19-10-15 06:16	19-10-15 10:49	19-10-15 15:12	20-10-15 06:15	20-10-15 09:58	20-10-15 14:50
Sodium (Na+)	144	**148**	**152**			**150**	**148**		**148**
Potassium (K+)	4.4	3.7	3.6			3.7	3.6		4.0
Chloride (Cl-)	98	106	**111**			**110**	107		**110**
Bicarbonate(HCO3-)	22	**18**	**16**			**17**	**18**		**16**
**Anion gap	**24.0**	**24.0**	**25.0**			**23.0**	**23.0**		**22.0**
CPK								64	
BUN	**160.9**	**148.6**	**154.7**				**148.0**		
Creatinine	**4.63**	**4.43**	**4.07**				**4.07**		
**eGFR(CKD-EPI equation)	11.74	12.38	13.72				13.72		
Triglyceride							**270**		
Total protein	7.7	6.9	6.5				6.5		
Albumin	**2.4**	**1.9**	**1.9**				**2.2**		
Globulin	**5.3**	**5.0**	**4.6**				**4.3**		
Total Bilirubin	**29.0**	**25.1**	**23.0**				**21.8**		
Direct Bilirubin	**24.24**	**22.01**	**21.18**				**20.31**		
AST (SGOT)	**64**	**54**	**61**				**64**		
ALT (SGPT)	**55**	**46**	**42**				41		
Alkaline (ALP)	**183**	**189**	**256**				**242**		
LDH							**661**		

Quickly identify patients who should be treated for leptospirosis is a challenge!

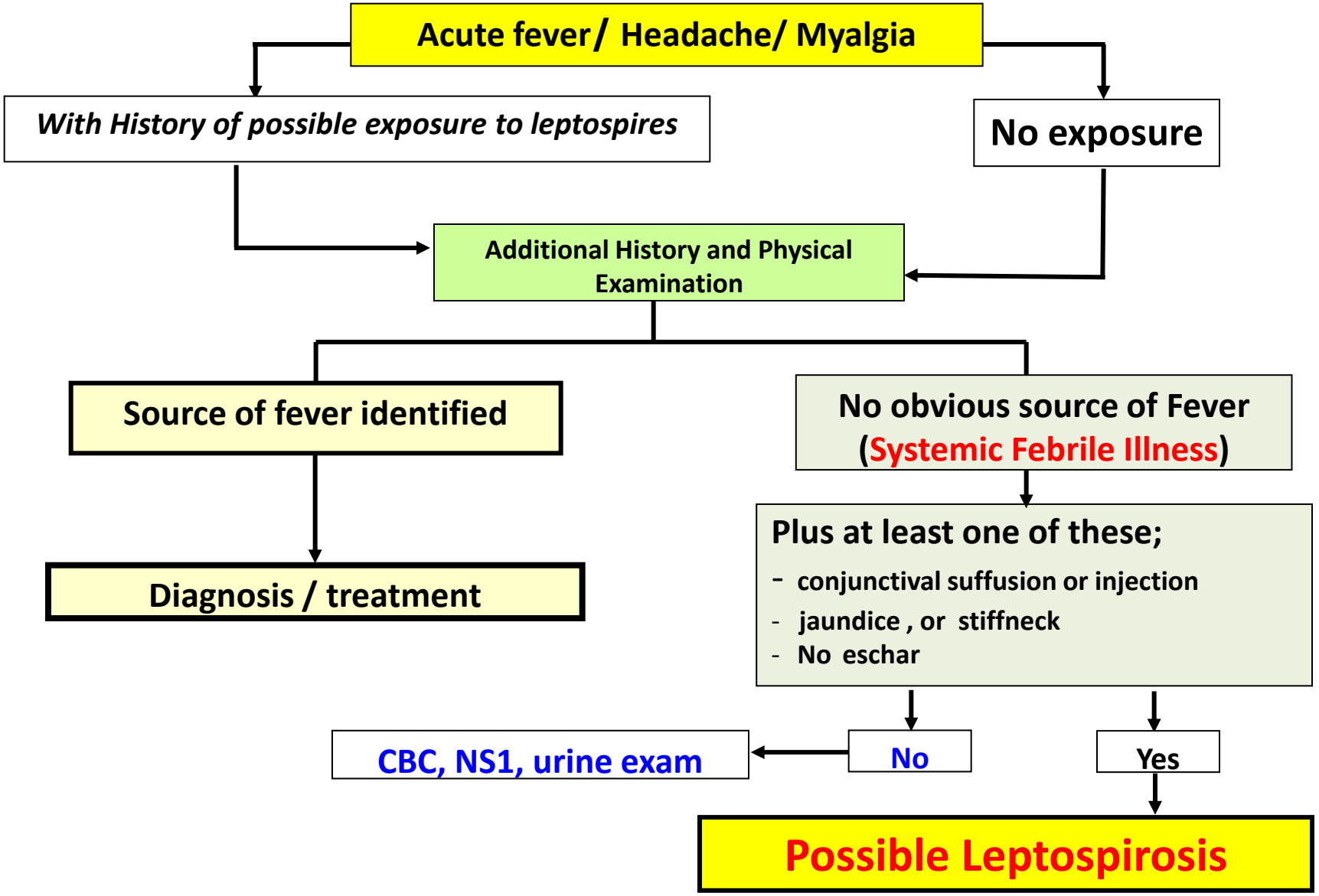
Clinical Practice Guideline

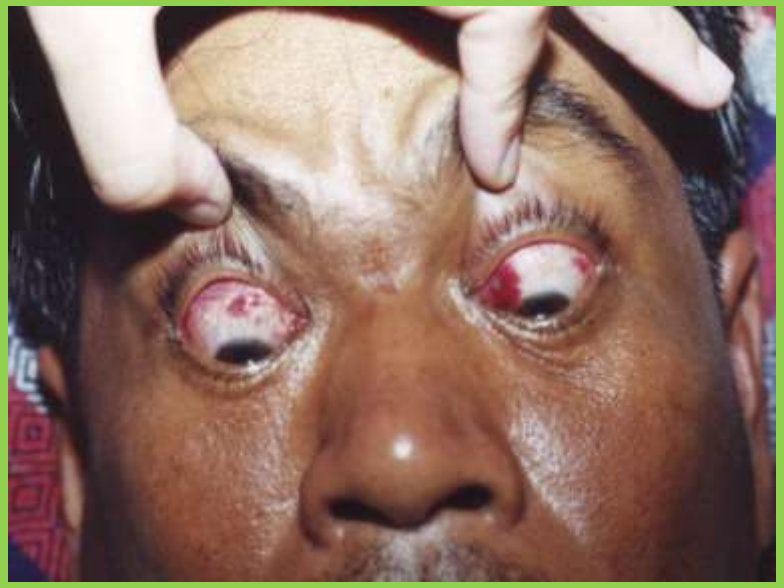
Acute Febrile Illness

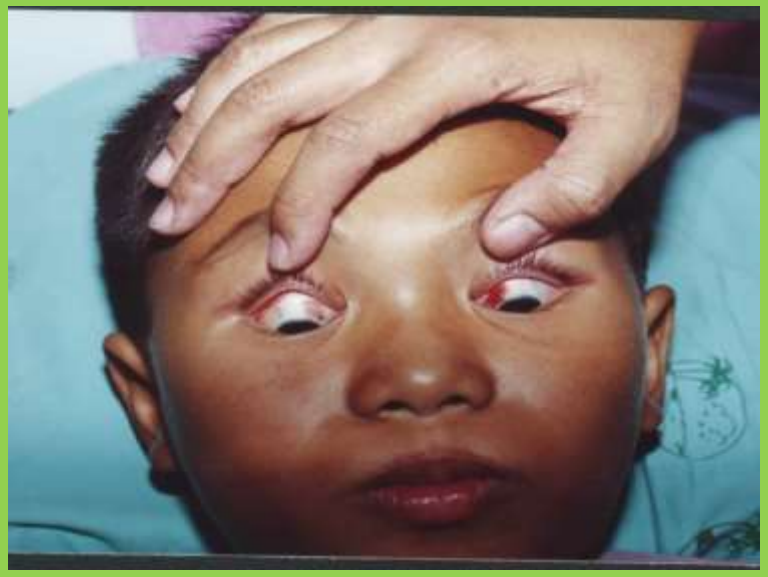


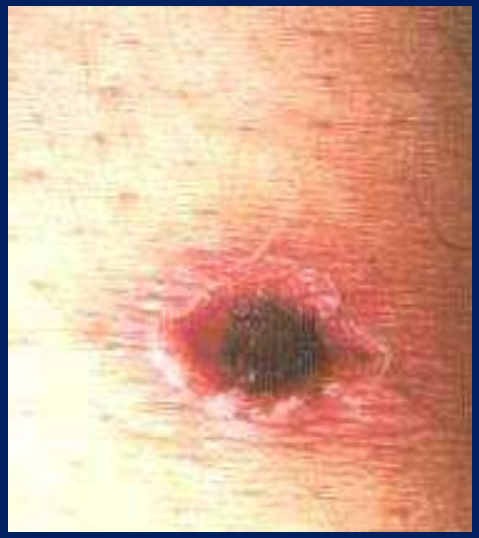


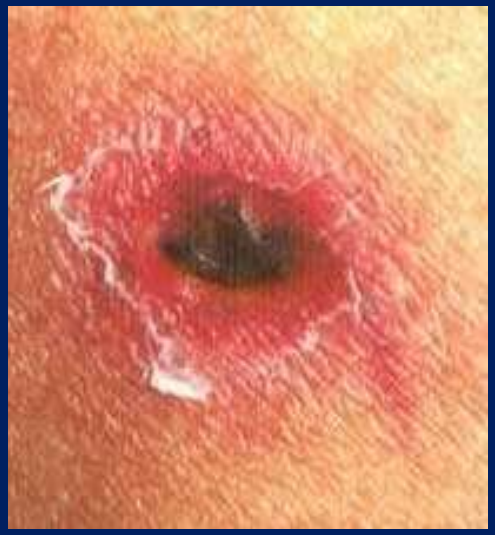
Early Diagnosis of Leptospirosis



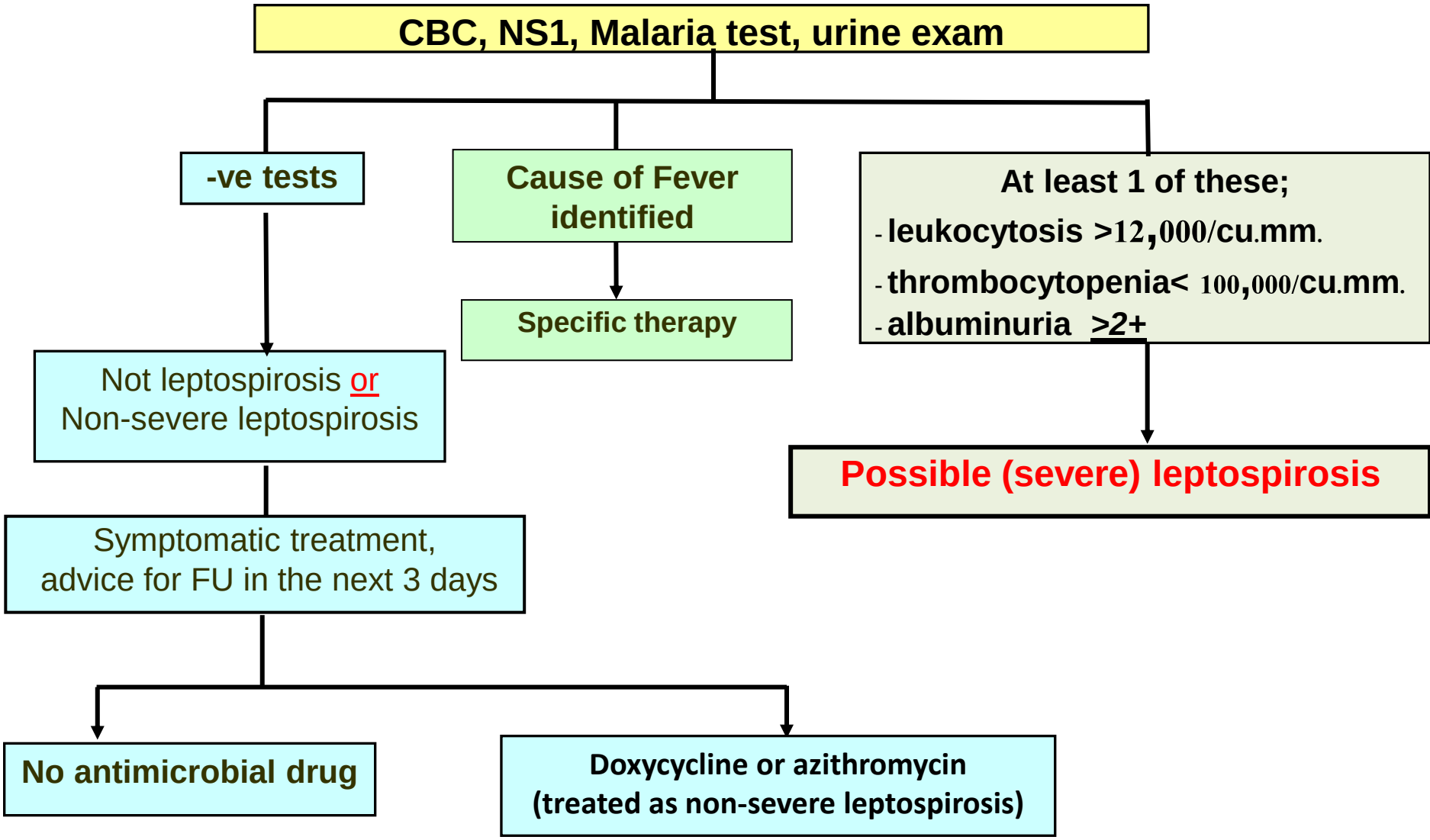








Early Diagnosis of Leptospirosis (cont.)



Management of possible leptospirosis

Possible Leptospirosis → **Laboratory tests**

↓

Perform Initial Clinical Assessment

↓

Any of the following?

- Pulse > 100/ min or irregular pulses
- hypotension (BP ≤ 90/60 mmHg) or pulse pressure < 20 mm.Hg
- RR ≥ 24 /min or dyspnea or abnormal CXR
- Jaundice or total birilubin > 2 mg/dl
- Decreased or no urine in the previous 8 hrs or serum creatinine> 2 mg./dl
- Abnormal bleeding
- Alteration of consciousness or stiff neck
- Platelet count < 100,000 /cum.
- WBC > 12,000 /cum.

No → **Non-severe leptospirosis**

1. Symptomatic treatment
2. Specific treatment
   2.1 doxycycline 100 mg. twice after meal or
   2.2 azithromycin 500 mg/d for 3 days
3. Advice for possible complication
4. **Advice for FU in 2-3 days**

↓ **Yes**

In patient Management or Refer

In- Patient management of possible leptospirosis

In-Patient management of possible leptospirosis

Supportive treatment and monitoring

- Volume replacement if hypotension
- Monitor vital signs, urine out put etc.

Empirical Antimicrobial drug

Choices of antimicrobial therapy

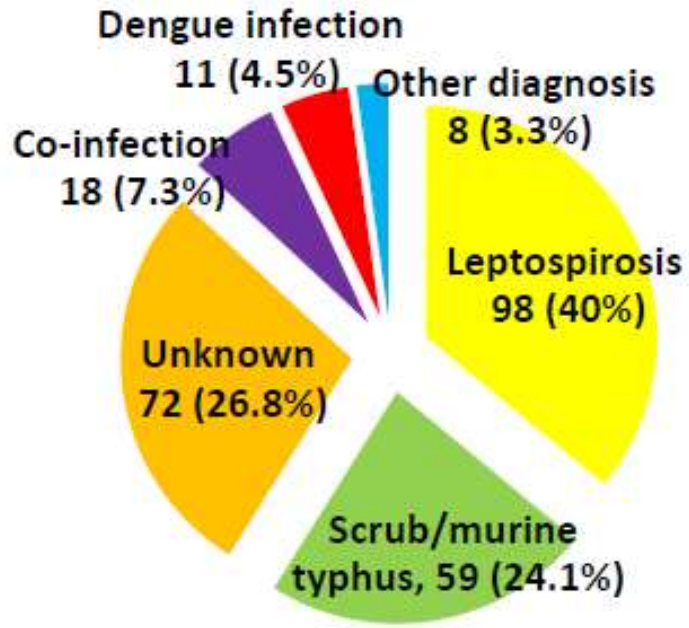
- Penicillin G Sodium 1.5 mu.q 6 hrs
- Ceftriaxone 1 gm IV OD
- Cefotaxime 1 gm IV q 6 hrs
- Azithromycin 500 mg IV OD
- Switch to oral drug to complete 7 days
- Advice for FU, and convalescence serological tests if possible

Deterioration or develop severe complication

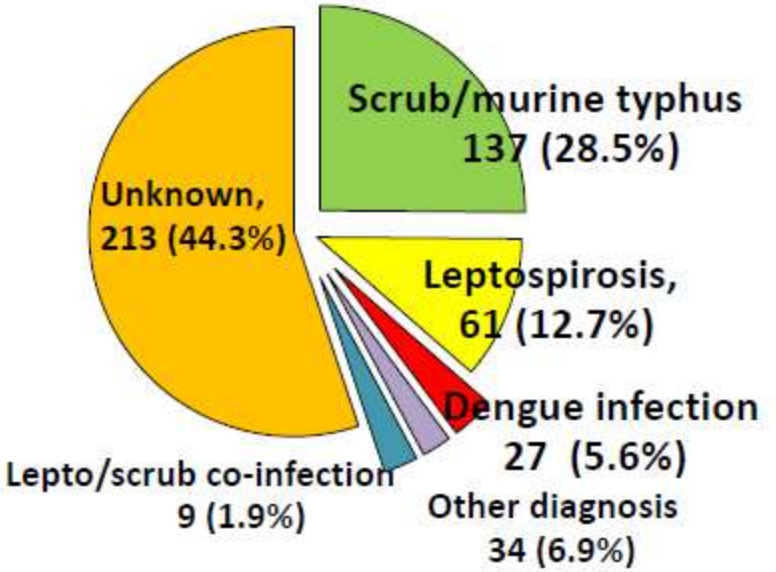
Refer or transfer for ICU Management

Causes of Acute Undifferentiated Febrile Illness (AUFI) : Korat Hospital

245 AUFI: Jul 2001-Dec 2002



481 AUFI: Jul 2011-Dec 2012



Clinical Manifestations

	2001-2002	2011-2012
Total number	98/245 (40%)	61/481 (12.9%)
Median Age, yrs	40 (18-75)	48 (19-75)
Sex	87:11	54:7
Days of fever, - Median (range) - Mean (SD)*	 4 (1-13) 5 (2.4)	 4 (3-13) 4 (1.4)
Case fatality*	6 (6.3%)	12 (19.7%)

Thipmontree W., et. al. 2014

Clinical Manifestations

	Survived (141)	Dead (18)	P-value
Age	48 (15-75)	50 (19-59)	0.8
Male, n (%)	125 (88.7)	16 (88.9)	0.9
Duration of fever	4 (1-13)	3 (3-10)	0.13
Severe complications, n (%)			
Hypotension/CVS	39 (27.9)	12 (66.7)	0.002
Abnormal LFT	95 (69.3)	15(83.3)	0.34
Acute kidney injury	95 (67.4)	14 (77.8)	0.532
Pulmonary involvement	36 (27.3)	12 (66.7)	0.002
Multi-organ dysfunction	44 (31.2)	14 (77.8)	<0.001
Thrombocytopenia	110 (78)	18(100)	0.027

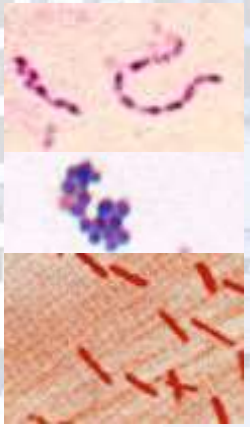
Acute Undifferentiated Fever (Systemic Infection)

Malaria

Dengue Infection

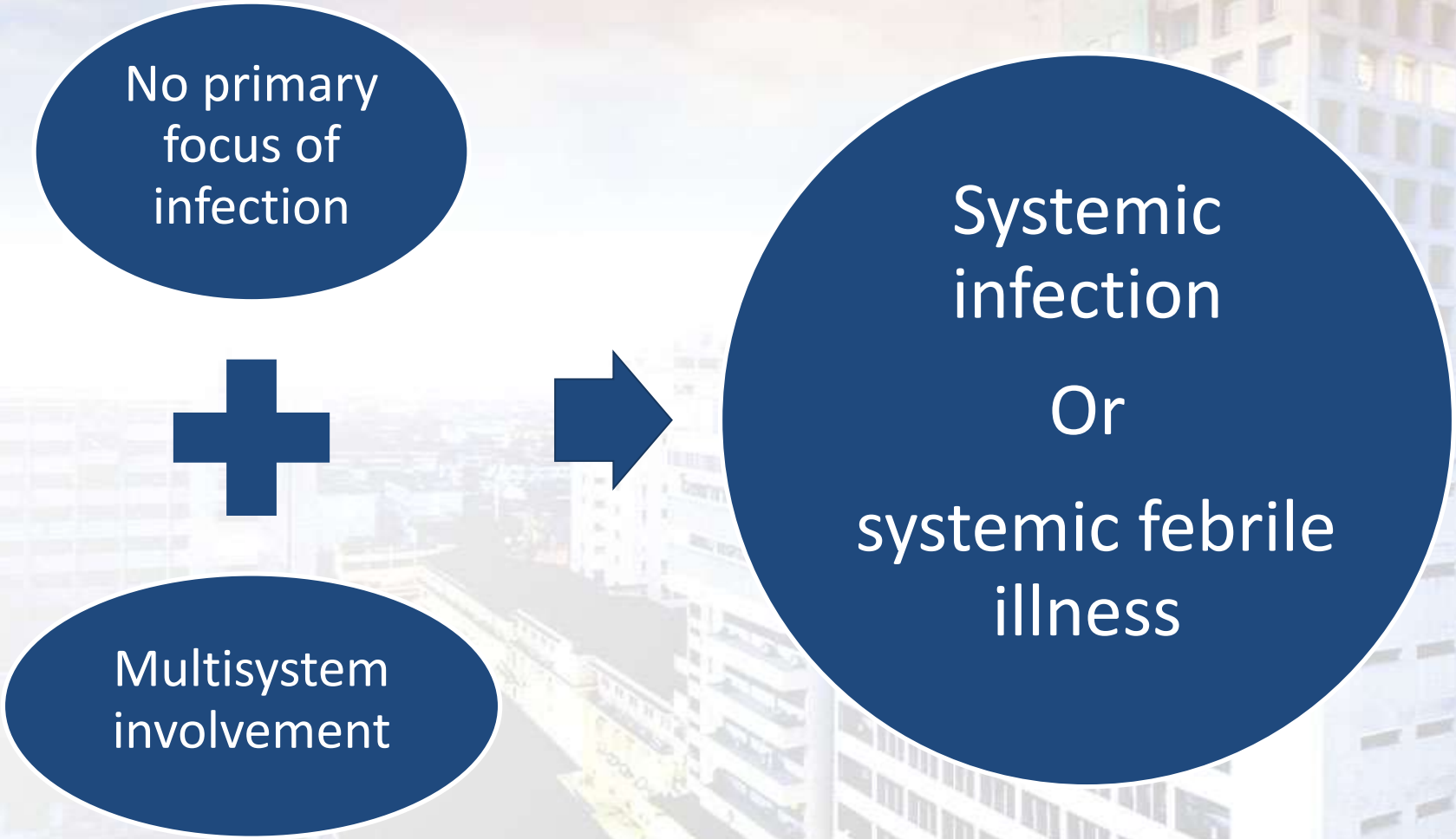
Rickettsioses

Leptospirosis



1^0 Bacteremia

Acute Undifferentiated Fever



Laboratory Diagnosis

Disease	Laboratory Test
Malaria	**Thick, thin blood smear, ICT (antigen test), PCR (*P. knowlesi*)**
Dengue infection	**CBC, IgG, IgM NS1 Ag, PCR**
Leptospirosis	**IFA, MAT, MCAT, ELISA, Culture, PCR**
Scrub typhus, Murine typhus	**IFA, Weil Felix test, PCR**
1^0 Bacteremia, salmonellosis etc.	**Blood culture**

Specific Treatment

Disease	Treatment
Malaria	**ACT (artemisinin combination therapy) such as artesunate+ mefloquine Chloroquine +/- primaquine**
Dengue infection	**No specific treatment**
Leptospirosis, 1^0 Bacteremia	**Penicillin, ceftriaxone, cefotaxime (ceftazidime), Doxycycline**
Scrub typhus, Murine typhus	**Doxycycline, chloramphenicol IV Azithromycin**

Strategies for Management of Acute Systemic Febrile Illness

Severity assessment

CBC, malaria, NS1

Investigations

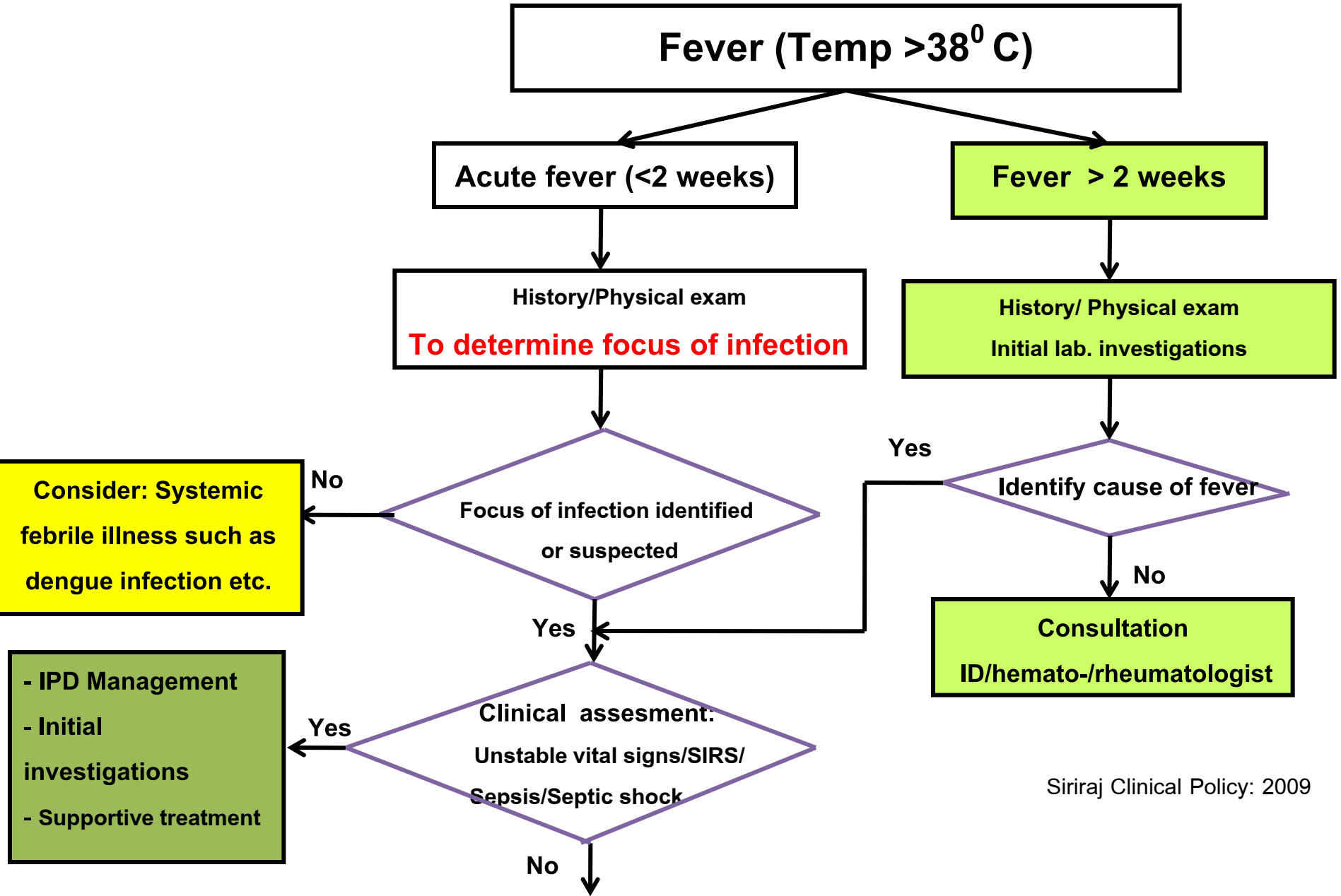
Follow up

Empirical therapy

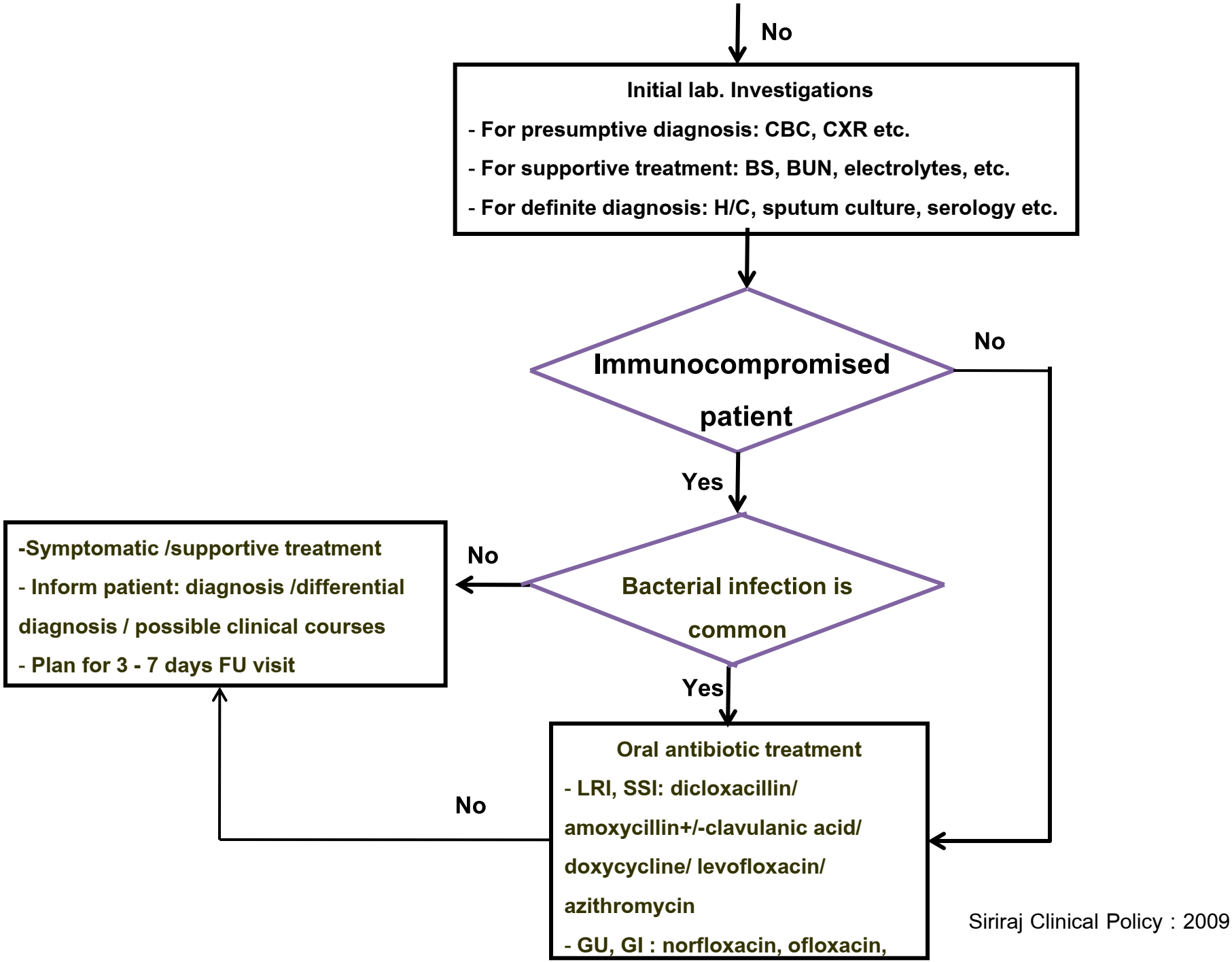
Mild: Doxycycline
Severe: Ceftriaxone + doxycycline, or azithromycin

Systemic Febrile Illness

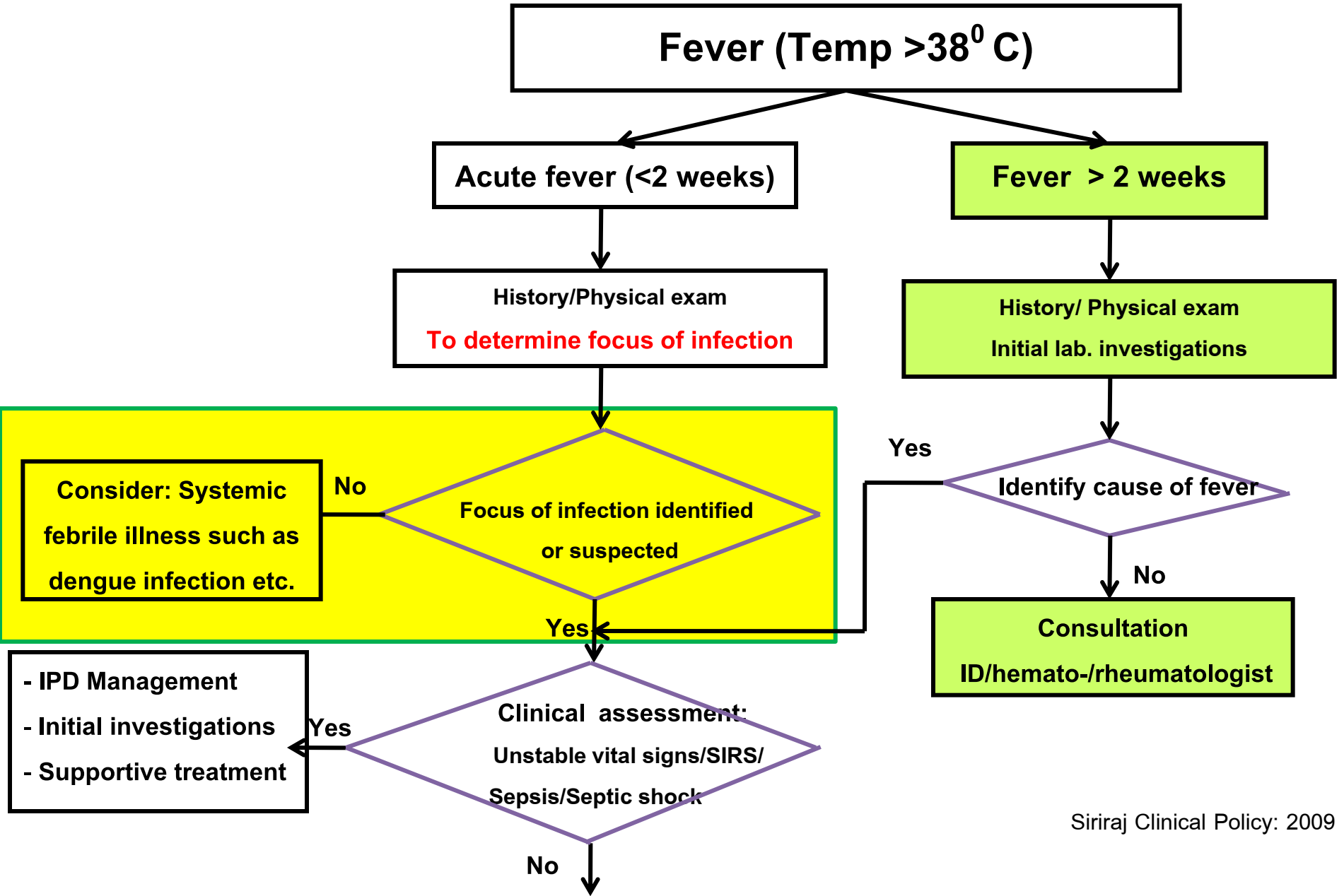
Acute Fever: Clinical Policy



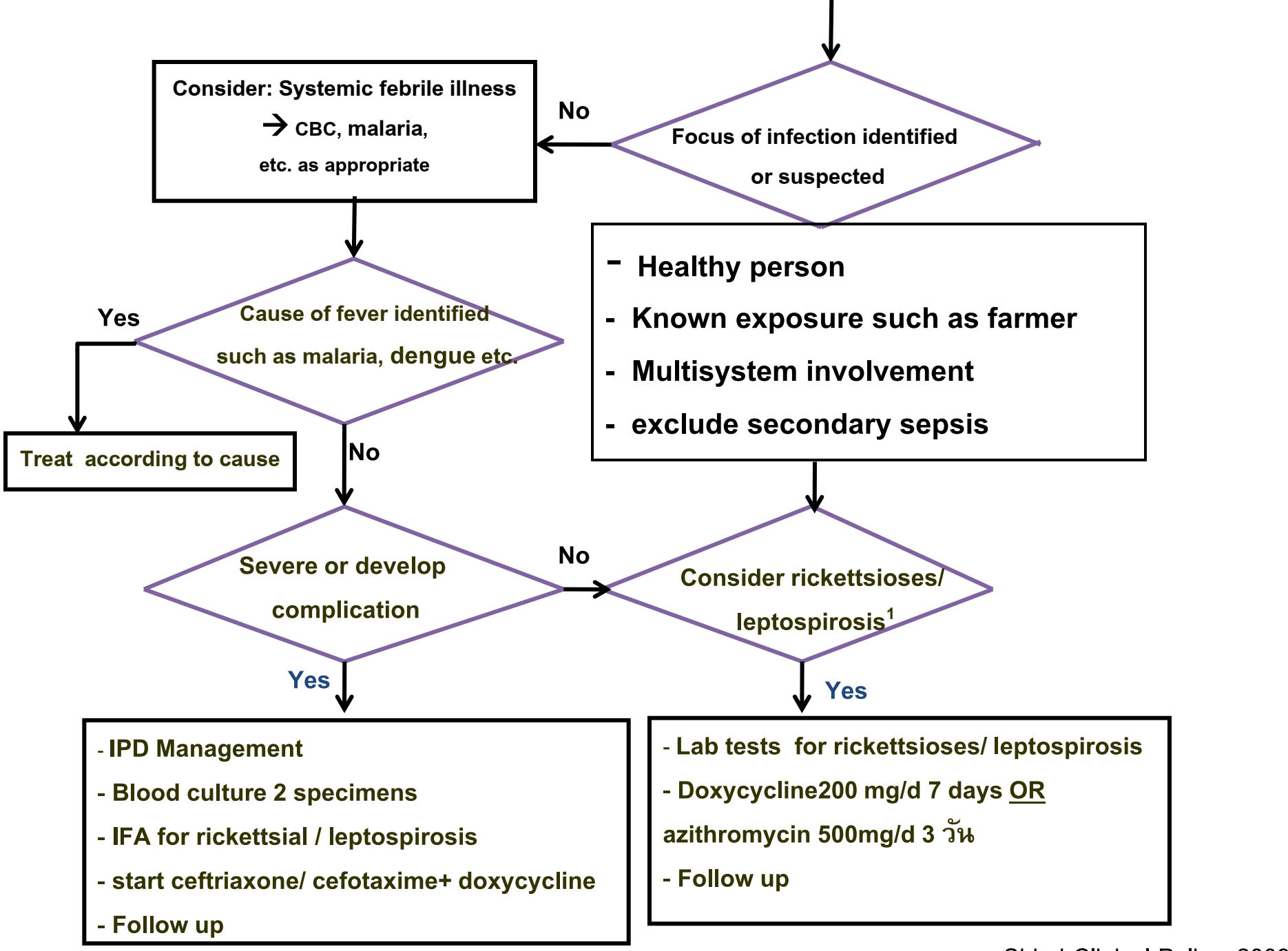
Siriraj Clinical Policy: 2009


No
Initial lab. Investigations
- For presumptive diagnosis: CBC, CXR etc.
- For supportive treatment: BS, BUN, electrolytes, etc.
- For definite diagnosis: H/C, sputum culture, serology etc.
Immunocompromised patient
No
Yes
Bacterial infection is common
No
-Symptomatic /supportive treatment
- Inform patient: diagnosis /differential diagnosis / possible clinical courses
- Plan for 3 - 7 days FU visit
Yes
Oral antibiotic treatment
- LRI, SSI: dicloxacillin/ amoxycillin+/-clavulanic acid/ doxycycline/ levofloxacin/ azithromycin
- GU, GI : norfloxacin, ofloxacin,
No
Siriraj Clinical Policy : 2009

Acute Fever: Clinical Policy



Siriraj Clinical Policy: 2009



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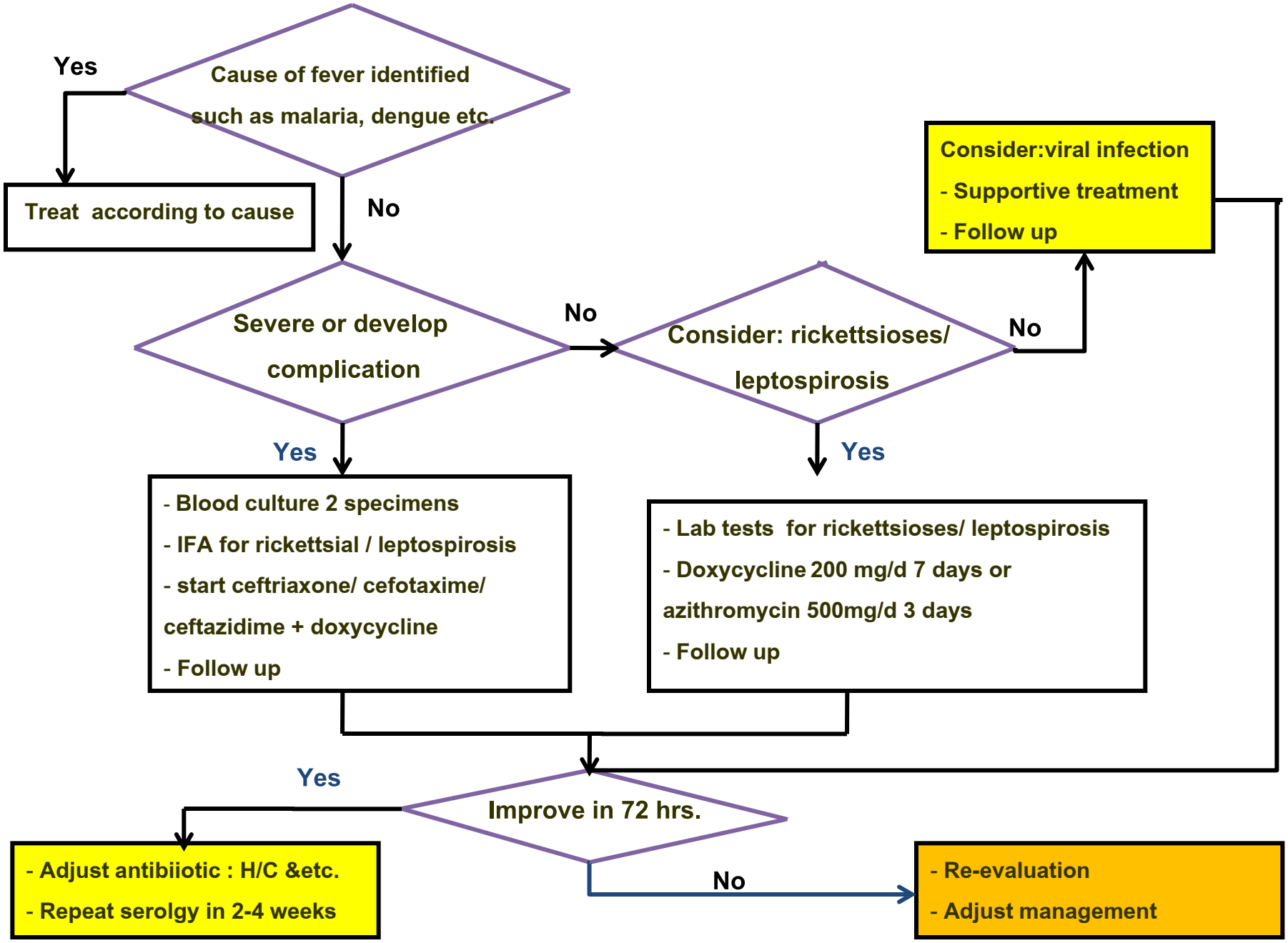

Siriraj Clinical Policy : 2009

Thank you
for your
attention

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Strategies for Diagnosis and Treatment of Suspected Leptospirosis: A Cost-Benefit Analysis

Yupin Suputtamongkol[1]*, Wirichada Pongtavornpinyo[2], Yoel Lubell[2], Chuanpit Suttinont[3], Siriwan Hoontrakul[4], Kriangsak Phimda[5], Kitti Losuwanaluk[6], Duangjai Suwancharoen[7], Saowaluk Silpasakorn[1], Wirongrong Chierakul[2], Nick Day[2]

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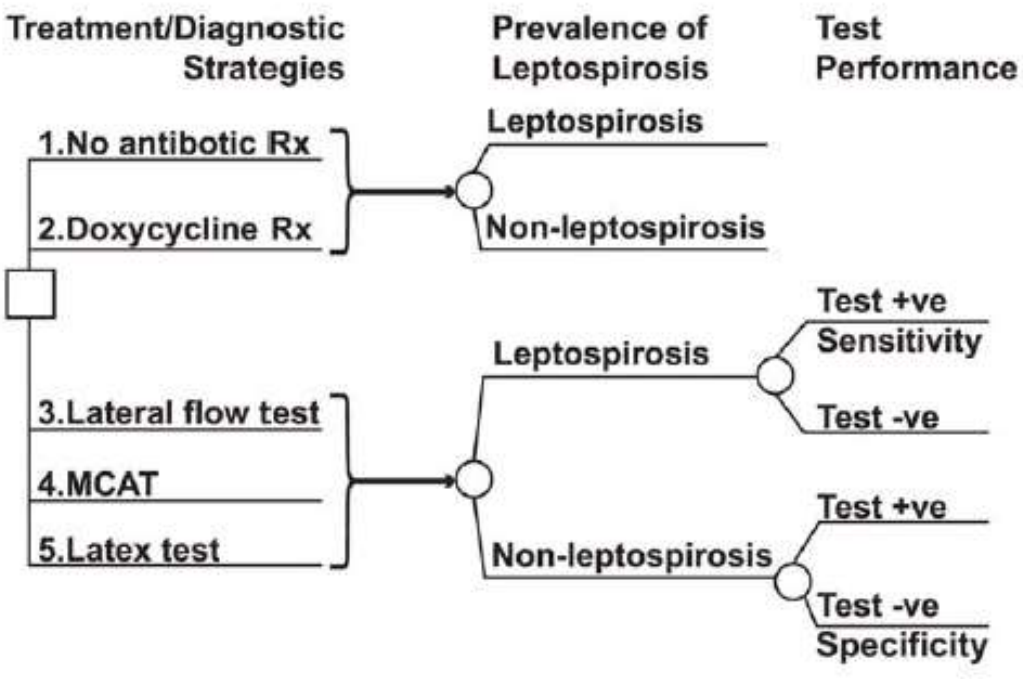
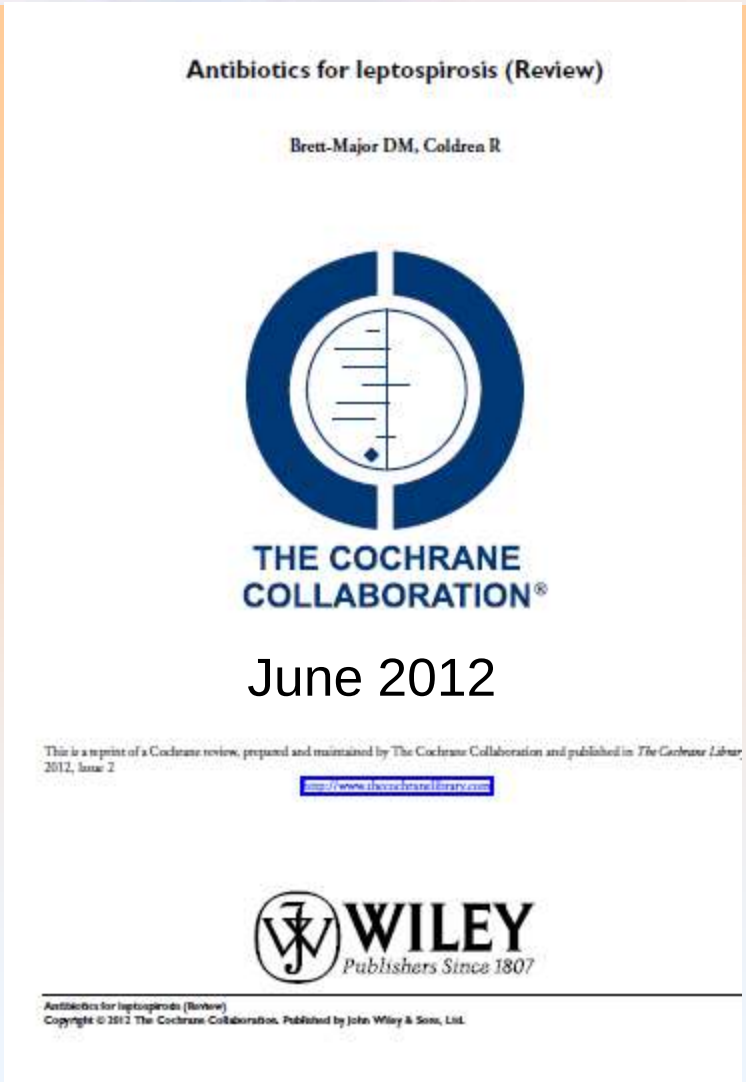


Antibiotic therapy for Leptospirosis



Insufficient evidence is available to advocate for or against the use of antibiotics in the therapy for leptospirosis.

Among survivors who were hospitalised for leptospirosis, use of antibiotics for leptospirosis may have decreased the duration of clinical illness by two to four days, though this result was not statistically significant.

When electing to treat with an antibiotic, selection of penicillin, doxycycline, or cephalosporin does not seem to impact mortality nor duration of fever.

Benefit of antibiotic therapy treatment of leptospirosis remains unclear, particularly for severe disease. Further clinical research is needed to include broader panels of therapy tested against placebo.

Antibiotic Therapy for Leptospirosis

- There remains uncertainty regarding the optimum antimicrobial therapy for severe leptospirosis
- Choices of antimicrobial therapy are
  - Penicillin G sodium
  - Ceftriaxone or cefotaxime
  - Doxycycline
- Neither high dose steroid nor desmopressin is effective as an adjunctive treatment of pulmonary hemorrhage associated with leptospirosis